

WHAT IS CLAIMED IS:

1. A non-naturally occurring bifunctional molecule of less than about 5000 daltons consisting of a drug moiety and a presenter protein ligand, wherein said drug moiety and
5 said presenter protein ligand are optionally joined by a linking group and said drug moiety has enhanced activity as compared to a free drug control.
2. The bifunctional molecule according to Claim 1, wherein said bifunctional molecule comprises a linking group.
- 10 3. The bifunctional molecule according to Claim 1, wherein said drug moiety exhibits at least one of enhanced affinity, specificity or selectivity for its target as compared to a free drug control.
- 15 4. The bifunctional molecule according to Claim 1, wherein said drug moiety binds to a protein target.
5. The bifunctional molecule according to Claim 1, wherein said presenter protein ligand binds to an extracellular protein.
- 20 6. The bifunctional molecule according to Claim 1, wherein said presenter protein ligand binds to an intracellular protein.
7. The bifunctional molecule according to Claim 6, wherein said presenter protein
25 ligand is a ligand for a peptidyl prolyl isomerase.
8. A synthetic bifunctional molecule of less than about 5000 daltons of the formula:

Z-L-X

wherein:

X is a drug moiety;

L is a bond or a linking group; and

Z is a ligand for an endogenous presenter protein ligand;

wherein X and Z are different and said drug moiety has enhanced activity as
5 compared to a free drug control.

9. The bifunctional molecule according to Claim 8, wherein said drug moiety
exhibits at least one of enhanced affinity, specificity or selectivity for its target as
compared to a free drug control.

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10. The bifunctional molecule according to Claim 8, wherein said drug moiety has a
molecular weight of from about 50 to 2000 D.

11. The bifunctional molecule according to Claim 8, wherein said drug moiety binds
15 to a protein target.

12. The bifunctional molecule according to Claim 8, wherein said presenter protein
ligand binds to an extracellular protein.

13. The bifunctional molecule according to Claim 8, wherein said presenter protein
20 ligand binds to an intracellular protein.

14. The bifunctional molecule according to Claim 13, wherein said presenter protein
ligand is a ligand for a peptidyl prolyl isomerase.

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15. The bifunctional molecule according to Claim 8, wherein said presenter protein
ligand has substantially no pharmacologic activity apart from binding to a presenter
protein ligand.

16. A method for producing a binary complex in a host, said method comprising:
administering to said host an effective amount of a bifunctional molecule of less
than about 5000 daltons consisting of a drug moiety and a ligand for a presenter protein
endogenous to said host, wherein said drug moiety and ligand are optionally joined by a
5 linking group;
whereby a binary complex comprising said bifunctional molecule and presenter
protein is produced that exhibits enhanced drug activity as compared to a free drug
control.
- 10 17. The method according to Claim 16, wherein said enhanced drug activity comprises
at least one of enhanced affinity, specificity or selectivity of said drug moiety for a target
of said drug moiety.
18. The method according to Claim 16, wherein said drug moiety binds to a protein
15 target.
19. The method according to Claim 16, wherein said presenter protein endogenous to
said host is naturally present at least in the region of said target.
- 20 20. The method according to Claim 16, wherein a tripartite complex is produced
between said bifunctional molecule, presenter protein and a target of said drug moiety,
wherein said tripartite complex is characterized by the presence of presenter protein target
binding interactions.
- 25 21. The method according to Claim 20, wherein said tripartite complex is produced
intracellularly.
22. The method according to Claim 20, wherein said tripartite complex is produced
extracellularly.

23. A method for producing a tripartite complex in a mammalian host, said method comprising:

administering to said mammalian host an effective amount of a bifunctional molecule of less than about 5000 daltons consisting of a drug moiety and a ligand for a presenter protein endogenous to said mammalian host, wherein said drug moiety and ligand are optionally joined by a linking group;

whereby said bifunctional molecule binds to a target of said drug and said presenter protein to produce said tripartite complex in said mammalian host, wherein said tripartite complex is characterized by the presence of presenter protein target binding interactions which result in enhanced drug activity as compared to a free drug control.

24. The method according to Claim 23, wherein said tripartite complex is produced intracellularly.

25. The method according to Claim 23, wherein said tripartite complex is produced extracellularly.

26. The method according to Claim 23, wherein said drug target is a protein.

27. The method according to Claim 23, wherein said endogenous presenter protein is selected from the group consisting of: peptidyl-prolyl isomerases, Hsp90, steroid hormone receptors, cytoskeletal proteins, albumin and vitamin receptors.

28. The method according to Claim 23, wherein said bifunctional molecule is administered as a pharmaceutical preparation.

29. A method for producing an intracellular tripartite complex in a mammalian host, said method comprising:

administering to said mammalian host an effective amount of a bifunctional molecule comprising a drug moiety and an endogenous presenter protein ligand, wherein the target of said drug and said endogenous presenter protein are intracellular proteins;

whereby said bifunctional molecule binds to said drug target and endogenous presenter protein to intracellularly produce said tripartite complex, wherein said tripartite complex is characterized by the presence of presenter protein target binding interactions which result in enhanced drug activity as compared to a free drug control.

30. The method according to Claim 29, wherein said target protein is an enzyme

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31. The method according to Claim 29, wherein said endogenous presenter protein is selected from the group consisting of: peptidyl prolyl isomerases, Hsp90, steroid hormone receptors and cytoskeletal proteins.

15 32. The method according to Claim 31, wherein said endogenous presenter protein is a peptidyl prolyl isomerase.

33. A method for producing a binary complex in a host, said method comprising:
administering to said host an effective amount of a bifunctional molecule
20 comprising a drug moiety and a ligand for a presenter protein endogenous to said host;
whereby a binary complex comprising said bifunctional molecule and presenter protein is produced that exhibits enhanced specificity for a target of said drug moiety target as compared to a free drug control.

25 34. The method according to Claim 33, wherein said ligand for a presenter protein is a peptidyl prolyl isomerase.

35. A method for enhancing the selectivity of a drug for a target in a first cell as compared to a second cell, said method comprising:

contacting said first and second cells with a bifunctional molecule comprising said drug and a ligand for a presenter protein present in said second cell but not in said first cell;

whereby a binary complex comprising said bifunctional molecule and presenter
5 protein is produced in said second cell but not said first cell.

36. The method according to Claim 35, wherein said drug moiety is an antimicrobial agent.

10 37. The method according to Claim 35, wherein said ligand is a peptidyl prolyl isomerase ligand.

38. In a method of administering a drug to a host in need of said drug, the
15 improvement comprising:

administering to said host an effective amount of a bifunctional molecule of less than about 5000 daltons consisting of said drug or a fragment thereof covalently linked, either directly or through an optional linking group, to a ligand for a presenter protein endogenous to said host.

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39. The method according to Claim 38, wherein said host is a mammalian host.

40. The method according to Claim 39, wherein said mammalian host is human.

25 41. The method according to Claim 38, wherein said drug is a small molecule.

42. The method according to Claim 38, wherein said drug binds to an extracellular target.

43. The method according to Claim 38, wherein said drug binds to an intracellular target.

44. The method according to Claim 43, wherein said presenter protein ligand is a
5 peptidyl prolyl isomerase.

45. A method of making a bifunctional molecule comprising a drug moiety that exhibits at least one of enhanced affinity, specificity or selectivity as compared to the corresponding free drug, said method comprising:

10 identifying a drug moiety;

preparing a library of bifunctional molecules comprising said drug moiety and a ligand for a presenter protein, wherein each bifunctional molecule shares a common ligand and drug moiety separated by a variable linking; and

15 screening said library to identify those members having at least one of enhanced affinity, specificity or selectivity as compared to the corresponding free drug.

46. A pharmaceutical preparation comprising a bifunctional molecule according to Claim 1.

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47. A kit comprising the pharmaceutical preparation according to Claim 46 and instructions for use in a therapeutic method.